REMARKS

Claims 23-31 and 33-43 are now pending in the application. Independent claim 31 is amended to include features from dependent claim 32. The Examiner is respectfully requested to reconsider and withdraw the rejections in view of the amendments and remarks contained herein.

1. INTERVIEW SUMMARY

Applicant's representatives would like to thank Examiner Fay for the courtesies extended during the telephonic interview on March 5, 2008.

The primary point of discussion was the 102 rejection under Viegas and the application of the disclosed gels (see details in section 3, below). Applicant's position is that a thorough reading of Viegas fails to identify *any instance* where the gel is introduced into the eye (see sections 3.2, 3.3, and 3.4 below). Moreover, Applicant and the Examiner agreed that all twenty-two of the Examples provided in Viegas illustrate external application of the gel to the outside of the eye (e.g., external protective corneal shields, laser ablatable masks, or contact lenses). The Examiner expressed concern regarding traces of the gel entering the interior of the eye in such procedures. However, the present claims include an applying step where the composition is made to directly contact an interior portion of the eye (claim 23), an intraocular site (claim 31), or where the composition is applied to prevent the anterior chamber from collapsing during surgery and then the majority is removed (claim 39). Applicant believes that these affirmative applying steps and associated features, including removing the composition from the intraocular site or anterior chamber, distinguish the present claims from the Examples found in Viegas – even if the Examiner's unsupported theory of accidental introduction into the eye is correct.

Applicant also offered to provide an evidentiary declaration to support that the Viegas reference does not teach application to the interior of the eye. However, the Examiner indicated that such evidence would not be necessary. Applicant will proffer such a declaration in the event an appeal becomes necessary.

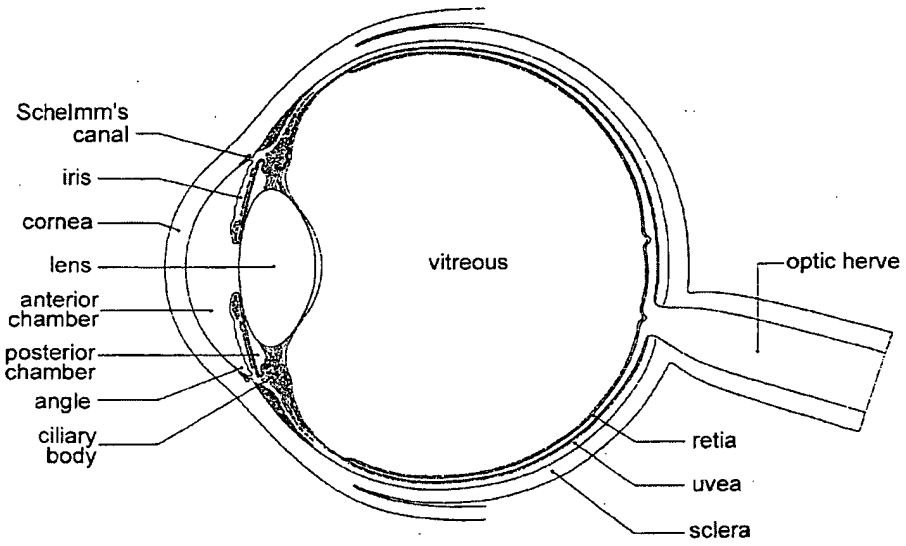
A secondary point of discussion was the 103 rejection (see details in section 4, below). Applicant appreciates the opportunity to elaborate the unique and previously

unknown problem relating to applying a viscoelastic substance to the interior of the eye (see section 4.2, below). Namely, upon application, the viscoelastic substance can enfold bacteria which are then protected or shielded within the eye from conventionally applied antimicrobials, such as antibiotic eye-drops or oral antibiotics. Identification of the unique problem led Applicants to construct the present solutions that include a viscoelastic substance mixed with an antimicrobial. Applicant appreciates the discussion of this unique problem with the Examiner as it serves to highlight the failures of conventional methods and demonstrates how Applicant's claims deal with this particular and unique source of infection at the most requisite time and site.

Finally, evidence of secondary considerations were discussed. While no agreement was reached, the Examiner did seem to indicate that the section 102 rejection could not stand and that more favorable consideration of this application was likely after she fully considers Applicant's position and discusses the issues with her colleagues.

2. Background and Summary of Claims

Independent claims 23 and 31 are drawn to methods for preservation and/or treatment against bacterial infection and/or inflammation in an ophthalmological surgery site, and independent claim 39 is drawn to a method for preservation and/or treatment against infection and/or inflammation during cataract surgery. These claims have in common a step where a pharmaceutical composition is applied to an interior portion of the eyeball. In particular, the pharmaceutical composition is applied to the anterior chamber, endothelium of cornea, lens capsule, and/or the passage of aqueous humor, which are illustrated in the following cross-sectional view of the eye:



The applied pharmaceutical composition includes a viscoelastic substance and an antimicrobial agent mixed in the viscoelastic substance. During eye surgery, the viscoelastic substance prevents collapse of an internal chamber of the eye, such as the anterior chamber, due to pressure loss caused from the outward flowing aqueous humor. Paragraphs [0009] and [0048]. The viscoelastic substance can be used in cataract surgery or during implantation of an artificial lens and can be used to protect the endothelium of the cornea during ultrasonic emulsification suction. Paragraph [0006].

There is a chance that an infectious microbe may be introduced into the eye during a surgical procedure. Paragraphs [0011] and [0022]. To combat the chance of post-operative infection, it is conventional to administer an antibacterial agent. Typically the antibacterial agent is administered systemically, either orally or intravenously, or is administered locally using an ophthalmic solution. Paragraph [0011]. Infection can lead to conditions such as endophthalmitis, involving inflammation of the intraocular cavities (i.e., the aqueous or vitreous humor), and may lead to other complications including blindness. Paragraph [0012]. Thus, it is paramount to prevent post-surgical infection.

Applicants have identified that the viscoelastic substance itself can play a unique role in post-operative infection. The viscoelastic substance can enfold bacteria introduced into the eye, thereby surrounding the bacteria and actually protecting the bacteria from in vivo biological attacks such as disinfection and sterilization. Paragraphs [0014] and [0091]. Protection of the bacteria by the viscoelastic substance

is further compounded by the fact that the half-life of the viscoelastic substance can be several hours. Paragraph [0010]. When bacteria are enveloped by the viscoelastic substance, systemic or locally applied antibacterial agents cannot contact the bacteria and these conventional methods to treat infection may be inadequate in this case.

In recognition and appreciation of this unique and heretofore unknown problem, Applicants devised the present inventive methods that utilize a viscoelastic substance with an antimicrobial agent mixed in the viscoelastic substance. Paragraph [0022]. Thus, if the viscoelastic substance introduced during surgery is responsible for the deposition and proliferation of bacteria in the eye, mixing an antimicrobial agent in the viscoelastic substance can prevent the bacteria from eluding physiological disinfection and sterilization. Paragraphs [0022] and [0052]. The present invention therefore presents the antimicrobial agent at the most requisite time and site to prevent infection as compared to conventional treatments. Paragraph [0096].

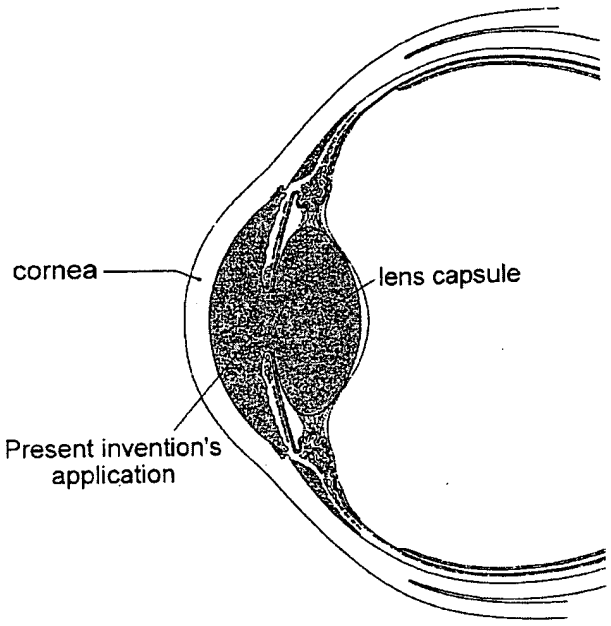
3. REJECTION UNDER 35 U.S.C. § 102

Claims 23, 24 and 26 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Viegas et al. (U.S. Pat. No. 5,587,175). This rejection is respectfully traversed.

Claims 23, 24, and 26 are drawn to methods that include applying a pharmaceutical composition containing a viscoelastic substance and an antimicrobial agent mixed in the viscoelastic substance. The applying step makes the pharmaceutical composition directly contact an anterior chamber, endothelium of cornea, lens capsule and a passage of aqueous humor, which are internal portions of the eyeball. In contrast, the Viegas reference only discloses application to external portions of the eyeball. As such, Viegas does not teach the claimed features and cannot anticipate the present claims. See *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (each and every element in the claim must be present in the reference for the claim to be anticipated).

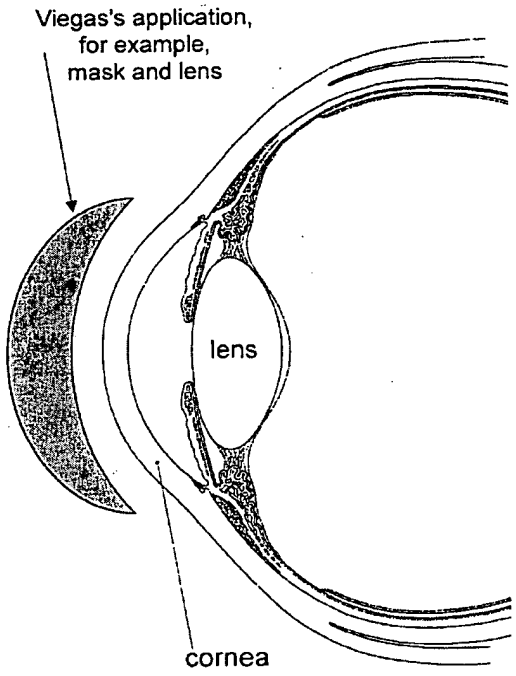
3.1 The present claims are directed to *internal* application in the eye.

The present claims include internal application of a pharmaceutical composition to an anterior chamber, endothelium of cornea, lens capsule, and a passage of aqueous humor. Internal application of the composition is illustrated in the following figure:



3.2 The Viegas reference is directed to *external* application on the eye.

In contrast to the present invention, the Viegas reference only teaches topical application to the eyeball, including processes employing protective corneal shields or laser ablatable masks to cover the outside of the eye. Ophthalmic application according to the Viegas disclosure is illustrated in the follow figure:



In particular, the Viegas reference refers to the following ophthalmic applications: delivery to the eye of a mammal (abstract); ophthalmic corneal protective devices and surgical device for corneal ulcers, etc. (col. 1, lines 12-13); ophthalmic areas of the mammalian body (col. 4, line 62); protective corneal shield (col. 4, line 67); ablatable corneal mask in laser keratectomy (col. 5, lines 1-2); ophthalmic areas of exposed tissue, gel can be peeled away or allowed to be absorbed (col. 5, lines 45-50); gel can be adjusted to pH of lacrimal tears (col. 6, lines 14-15); ophthalmic drug delivery compositions, laser ablatable shields, corneal protective compositions (col. 8, lines 37-39); applied to cornea (col. 8, lines 47-48); corneal protective shield (col. 9, line 15); ophthalmic drug delivery vehicle, laser ablatable corneal mask, and corneal protective compositions of the invention (col. 10, lines 63-65); corneal mask compositions of the invention (col. 11, line 25); laser ablatable corneal mask (col. 11, line 38); corneal mask (col. 11, line 44); Examples 1-5 include laser ablatable corneal mask or protective corneal shield; Examples 11-15 include application to rabbit cornea; Example 18 includes a medicated contact lens; and Examples 19-22 include laser ablatable corneal mask or protective corneal shield.

There is no disclosure anywhere in the Viegas reference of applying the composition to the interior of the eyeball.

3.3 The Viegas reference discloses injection or internal application in a body cavity to separate tissues or organs – not the eye.

The Viegas reference does not teach any method where the composition is applied to an internal portion of the eyeball and therefore cannot anticipate the present claims. For example, there is no disclosure of internal ophthalmological applications such as cataract or glaucoma surgeries. Instead, the injection or body cavity applications taught in Viegas are disclosed only as alternate embodiments, where the gel serves as a drug depot or to separate organs during a surgical procedure in order to prevent adhesions.

In particular, the Viegas reference refers to the following internal applications: topical body cavity or injection application of drugs or diagnostic agents (abstract); compositions without drug are useful as medical device for separating surgically or otherwise injured tissue to prevent adhesions (abstract); drug delivery system, prevention of post-surgical adhesions (col. 1, lines 11-12); topical, injection, or body cavity delivery (col. 4, line 58); injectable compositions for depot drug delivery (col. 4, lines 66-67); and as a medical device for separation of organs, prevention of adhesions (col. 5, lines 3-5).

Thus, the only disclosed internal applications are using the composition to separate tissue or organs to prevent adhesions (i.e., scar tissue formation) or to act a drug depot. There is no disclosure regarding the application of the composition to an interior portion of the eye or using the composition in internal procedures such as cataract or glaucoma surgeries within the eye.

3.4 The Viegas Examples are *all* directed to *external* applications to the eye.

It is of particular note that there is not one working example in the Viegas disclosure of applying the Viegas composition to an internal portion of the eyeball. All twenty-two of the detailed Examples are instead teaching external protective corneal shields or laser ablatable masks or a contact lens. These examples are entirely different than the presently claimed methods; compare illustrative figures in Sections 3.1 and 3.2, presented above.

3.5 The Viegas reference fails to disclose all the claimed features.

In sum, the Viegas reference is silent regarding a method for preservation and/or treatment against bacterial infection and/or inflammation in an ophthalmological surgery site that comprises applying a pharmaceutical composition containing a viscoelastic substance as a surgical protecting agent for ophthalmology and an antimicrobial agent mixed in the viscoelastic substance, so as to make the pharmaceutical composition directly contact an anterior chamber, endothelium of cornea, lens capsule and a passage of aqueous humor. Viegas simply discloses the external application of the composition to the exterior of the eye. And notably, when viewing the reference teachings as a whole, it is clear that application to a body cavity by injection is separate from external application to the cornea of the eyeball, as these features of Viegas are set out separately and are not coextensive. There is not one instance in Viegas among the many ophthalmic examples where the composition is used within the interior of the eye or in conjunction with an internal surgery. Hence, Viegas does not teach applying a viscoelastic substance internally and is therefore not an anticipatory reference.

Applicant respectfully requests reconsideration of the claims and withdrawal of the rejection.

4. Rejection Under 35 U.S.C. § 103

Claims 25 and 27-43 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Viegas et al. (U.S. Pat. No. 5,587,175) in view of Chang (U.S. Pat. No. 6,051,560) and further in view of Christ et al (U.S. Pat. No. 6,254,587). This rejection is respectfully traversed.

Independent claims 23, 31, and 39 are drawn to methods for preservation and/or treatment against infection and/or inflammation during ophthalmic surgery. Each includes an applying step, where a viscoelastic substance mixed with an antimicrobial or anti-inflammatory agent is applied to an internal portion of the eyeball. In contrast, the combination of the Viegas, Chang, and Christ references fails to provide an apparent reason for a person of ordinary skill in the art to combine and modify the teachings therein so as to recreate at least this feature of Applicants' claims. In

addition, there is no appreciation in the combined references or in the general knowledge in the art at the time the invention was made of the problem posed by the enfolding of infectious bacteria within the viscoelastic substance. As such, construction of the presently claimed methods using the cited references is only possible in hindsight. The present claims are therefore not obvious.

4.1 No reason exists for making the alleged combination.

Combination of Viegas, Chang, and Christ cannot render the presently claimed methods obvious as there is no apparent reason evident in the references themselves or based on the general knowledge in the art by which a skilled artisan would combine and modify their teachings as alleged in the rejection. See *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1734, 82 USPQ2d 1385, 1391 (2007) (obviousness includes determining whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue); *In re Kahn*, 441 F3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning to support the legal conclusion of obviousness.").

These three references do not appreciate the particular issues of infection by exogenous bacteria within an intraocular space that are addressed by the present invention. Only Applicants' methods afford antimicrobial properties to residual traces of viscoelastic substance left within the eyeball that may enfold infectious bacteria. The present inventive methods consequently do not shield bacteria from the antimicrobial agent, as is the case with separately administered antibiotics. Consequently, there is no reason for a skilled artisan to adapt the external protective corneal shields, laser ablatable masks, or contact lens as taught by Viegas for use in an internal application as disclosed by Chang and Christ.

As described above in Section 3, Viegas teaches a process using a gel composition having an antibacterial substance as a corneal mask or shield to protect the cornea exterior during excimer laser keratectomy or as a contact lens. All description in the Viegas disclosure relating to ophthalmic applications involves external uses of the gels. All of the twenty-two examples further serve to illustrate that with

respect to applications to the eye, the gel is only used on the eye exterior. See illustrative figures in above Sections 3.1 and 3.2. As a result, the Viegas reference is silent regarding residual traces of viscoelastic substance within the eye or issues relating to protection of introduced bacteria that are enveloped in viscoelastic substance.

Chang teaches high viscosity compositions used to maintain the corneal dome and protect corneal endothelial cells during intraocular lens implantation surgery. See Chang col. 1, lines 58-65; lines 30-33; and lines 45-50. The reference does not teach mixing an antimicrobial or anti-inflammatory with the viscous composition. Furthermore, Chang is silent regarding infection issues arising from introduced bacteria becoming enfolded in the viscous composition and protected thereby.

The Christ reference teaches a method for delivering a viscoelastic material to an eye. Christ abstract; col. 1, lines 46-60. However, the Christ disclosure is silent regarding applying a viscous gel-like composition mixed with an antimicrobial agent into the interior of the eye. Moreover, the Christ disclosure fails to appreciate the problem of enfolding infectious bacteria within the viscous gel-like composition thus protecting the bacteria within the eye.

In sum, there is no established basis or apparent reason for a skilled artisan to combine the Viegas, Chang, and Christ teachings as alleged. Likewise, the present rejection fails to provide an apparent reason based on the general knowledge in the art to act as a nexus by which a skilled artisan would so combine these three references. Nothing in reference combination speaks to the desirability of using the Viegas gel composition within an intraocular space.

4.2 Only the present invention recognizes the problem resulting from enfolding introduced bacteria in a viscoelastic substance and provides methods to address the problem.

As noted and cited in MPEP § 2141.02, "a patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. This is part of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35

U.S.C. § 103." *In re Sponnoble*, 405 F.2d 578, 585, 160 USPQ 237, 243 (CCPA 1969) (emphasis in original).

> In *In re Sponnoble*, the claim was directed to a plural compartment mixing vial wherein a center seal plug was placed between two compartments for temporarily isolating a liquid-containing compartment from a solids-containing compartment. The claim differed from the prior art in the selection of butyl rubber with a silicone coating as the plug material instead of natural rubber. The prior art recognized that leakage from the liquid to the solids compartment was a problem, and considered the problem to be a result of moisture passing around the center plug because of microscopic fissures inherently present in molded or blown glass. The court found the inventor discovered the cause of moisture transmission was through the center plug, and there was no teaching in the prior art which would suggest the necessity of selecting applicant's plug material which was more impervious to liquids than the natural rubber plug of the prior art.
> (MPEP § 2141.02, III. Discovering Source/Cause of a Problem is Part of "As a Whole" Inquiry)

In the present case, Applicants have identified a unique mechanism by which internal application of the viscoelastic substance can contribute to post-operative infection. Application of the viscoelastic substance can enfold bacteria introduced into the eye, surrounding the bacteria and protecting the bacteria from in vivo biological attacks such as disinfection and sterilization. See present specification, paragraphs [0014] and [0091]. Protection of the bacteria by the viscoelastic substance is compounded further by the fact that the half-life of the viscoelastic substance can be several hours. See present specification, paragraph [0010]. When bacteria are enveloped by the viscoelastic substance, systemic or locally applied antibacterial agents cannot contact the bacteria and these conventional methods to treat infection may be inadequate.

Applicants respectfully direct the Examiner's attention to the present application as substantiating evidence for the discovery of the source of the infection problem posed by internal application of a viscoelastic substance. The specification illustrates that traces of viscoelastic substance can remain within the intraocular space following surgery. Paragraph [0009]. The residual traces can enfold bacteria and keep them from in vivo biological attacks. Paragraph [0014]; see also background and summary of claims in Section 2 above. Example 1 demonstrates that a viscoelastic substance may

be contaminated with bacteria based on the fact that Healon® (a solution of sodium hyaluronate; i.e., a viscoelastic substance) has neither bacterial proliferation accelerating activity nor proliferation suppressing activity. Paragraphs [0064] and [0065]; and see FIGS. 1 and 2. Example 2 demonstrates that the viscoelastic substance may trap an antimicrobial agent and inhibit it from locomotion. Paragraph [0089]. The viscoelastic substance can therefore contact bacteria with the antimicrobial in the event bacteria are enfolded within the residual traces of the substance. Efficacy of the antimicrobial agent can be completely maintained when it is mixed with the viscoelastic substance, and since the antimicrobial is not released, it can prevent bacterial deposition caused by the viscoelastic substance. Paragraphs [0093]-[0095] and [0091]; and see FIGS. 4 and 5.

Applicants also submit the publication by Koichiro Tanaka et al., *Incidence and Prevention of Bacterial Endophthalmitis with the Use of Viscoelastic Materials and Newquinolone*, J. Med. Soc. Toho. Univ., Vol. 52 (5):303-316 (Sept. 2005), enclosed with this amendment, as additional support to substantiate Applicants' discovery of this unique problem and the surprising and unexpected results afforded by Applicants' invention. Briefly, this publication illustrates the effectiveness of "Antibacterial Visco" (a viscoelastic substance and mixed antimicrobial) in treatment of an endophthalmitis model. Infection is compared between an antibacterial visco group, an eye drop treatment group (containing antibacterial), a non-treatment group, and a bacteria inoculation group. See abstract and Section 3 on page 307. Table 5 demonstrates that "Antibacterial Visco" significantly reduces the rate of endophthalmitis after inoculation compared to the eye drop treatment. The reported results show clear advantages of Antibacterial Visco in preventing endophthalmitis and that antibacterial drug penetration is not decreased by admixture with viscoelastic material. Page 313, last paragraph of left column. The results also show that a small number of bacteria can cause bacterial endophthalmitis in the presence of viscoelastic material, and that the use of viscoelastic material makes antibacterial eye drop treatment ineffective by sheltering the bacteria from the drug. Page 313, first four paragraphs of right column.

In conclusion, Applicants submit that the present specification clearly identifies a heretofore unknown problem and provides the present inventive methods to treat the

problem. The above publication by Koichiro Tanaka et al. is further evidence as to the effectiveness of the present methods and serves to illustrate the unique mechanism of bacterial infection identified and addressed by the present claims.

4.3 The present invention provides unexpected results, satisfies a long-felt need, and is contrasted by the failure of others.

Applicants also wish to direct the Examiner's attention again to Exhibits A, B, C, and D that were provided with the Amendment filed February 12, 2007 as evidence of secondary considerations that distinguish the present claims from conventional methods used in ophthalmic surgery. These Exhibits touch on several important Graham Factors, namely unexpected results, long-felt need, and the failure of others. See *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) and MPEP § 2141. In particular, the Exhibits contrast the success of Applicants' invention and claims versus the unsatisfactory results or failure of conventional methods that apply a viscoelastic substance and *separately* apply an antimicrobial agent, as conventional in the art. Summaries of these exhibits were provided in Applicants' amendment filed August 31, 2007.

In view of the conventional methods, it is unexpected that mixing the antimicrobial with the viscoelastic substance would be better than applying these components separately since the mechanism of enfolding and protecting bacteria within the viscoelastic substance was unknown in the art. The conventional methods failed to appreciate and recognize that the viscoelastic substance can shield or block the separately applied antimicrobial from contacting the bacteria. Moreover, the conventional methods did not appreciate that residual traces of viscoelastic material can persist in the eye after substantially all the material is removed. By mixing antimicrobial with viscoelastic substance as in the present claims, the antimicrobial agent can act at the most requisite time and site and suppress bacteria associated or in contact with the residual traces of material. Consequently, Applicant's invention addresses a long-felt need to prevent ocular infections and overcomes the failures associated with conventional methods.

4.4 The alleged combination is constructed using impermissible hindsight.

At the time of Applicants' invention, there was no reason for a skilled artisan to combine the Viegas, Chang, and Christ references. No benefit would be expected to result as there was no appreciation in the art regarding the protective mechanism caused by enfolding bacteria in a viscoelastic substance. Thus, there is no basis for a person of ordinary skill to abandon or change the administration of separate antibiotics, whether systemically (e.g., oral) or locally applied (e.g., eye drops) as is conventional in the art. Applicants' discovery of the unique problem caused by bacteria enfolded in residual traces of viscoelastic substance and the appreciation as to how to address this route of infection led to the present claims. Thus, the only rationale for constructing the present rejection is by impermissibly using Applicants' invention as a template.

In seeking to establish obviousness, a combination of references cannot be constructed by using Applicant's disclosure. As stated by the court in *ATD Corporation v. Lydall, Inc.*, 159 F.3d 534, 48 USPQ2d 1321, 1329 (Fed. Cir. 1998):

> Determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. There must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor.

The present claims are therefore nonobvious, as the present rejection fails to establish an apparent reason to make the alleged combination based on Viegas, Chang, and Christ. "[R]ejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006).

In view of the preceding remarks, Applicant respectfully requests reconsideration of the claims and withdrawal of the rejection.